REMARKS/ARGUMENTS

Amendments to the Claims

This application contains claims 1, 4, 8-13, 15-32, 35-43, and 48-51. With this amendment, claims 45-47 have been canceled, without prejudice. Applicants expressly reserve the right to pursue any canceled subject matter in subsequent applications that claim benefit from this application. Claims 1 and 4 have been amended, and new claims 48-51 have been added to more particularly point out and distinctly claim the subject matter that Applicants wish to prosecute in this application. No new matter has been introduced. Reconsideration is respectfully requested.

Amended claim 1 recites N-terminal fragments of the AFT2 amino acid sequence as disclosed by the instant application. Support for amended claim 1 and added claims 48-51 may be found, for example, on page 3, lines 27-29 to page 4, line 1. To expedite prosecution and facilitate an allowance, Applicants have also amended claim 1 to cancel recitation of the word "wild-type." In their December 9, 2005 Amendment, Applicants added the word "wild-type" to clarify that Applicants disclose and claim N-terminal fragments of the AFT2 amino acid sequence that is normal or non-mutated. However, it is not necessary for amended claim 1 to recite "wild-type." Based upon a reading of the specification, the skilled worker would understand that it is silent with respect to specific mutations or alterations to an AFT2 amino acid sequence. Therefore, it would be clear to a skilled worker that Applicants teach N-terminal fragments of a non-mutated, normal AFT2 amino acid sequence. Thus, recitation of the word "wild-type" in amended claim 1 does not add any additional meaning that a skilled worker could not understand from a reading of the instant application or U.S. Provisional Application Nos.: 60/269,257 and 60/269,118.

Amended Claim 4 now reads as an independent claim. Support for amended claim 4 may be found, for example, on page 4, lines 14-17 of the specification as filed.

The issues raised by the Examiner in the Office Action are summarized and addressed below.

Election/Restrictions

The Examiner contends that claims 45-47 are directed to an invention that is independent or distinct from the invention originally claimed. The Examiner also contends claims 45-47 are directed to a method for inhibiting metastasis of a tumor cell, and are patentably distinct from the inventions of claims 1, 4, 8-12, and 35-43 that are drawn to a method for inhibiting the growth of tumor cells, claims 23-29 that are directed to a method for treating a tumor and claims 13, 15, 20, and 21 that are directed to a product, namely a polypeptide or a composition thereof.

In the sole interest of placing this case in candidate for allowance and without addressing the merits of this rejection, Applicants have canceled claims 45-47, without prejudice. Accordingly, Applicants request that the Examiner withdraw this restriction.

Priority

The Examiner acknowledges Applicants' claim under 35 U.S.C. § 119(e) for benefit of the earlier filing dates of U.S. Provisional Application No. 60/269,257, filed February 16, 2001, and U.S. Provisional Application No. 60/269,118, filed February 15, 2001. However, the Examiner contends that claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 do not properly claim benefit to the earlier filed provisional applications because those claims have been rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. For this reason, claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 have been deemed the filing date of the instant application, which is February 14, 2002. Applicants traverse.

In order to expedite prosecution and facilitate an allowance without conceding to the Examiner's rejection, Applicants' amendment of claim 1 renders the Examiner's rejection moot. The amended claims no longer recite "wild-type" because these claims directed to Applicants' invention do not require this word. In the instant application, Applicants disclose and claim

inhibitory N-terminal fragments of AFT2 having a normal or endogenous amino acid sequence. Applicants request reconsideration and withdrawal of this objection.

Objection to the Claims

The Examiner has objected to claims 4 and 12 because the claims recite "the inhibitory N-terminal fragment of ATF-2" as opposed to "the inhibitory N-terminal fragment of wild-type ATF-2".

Applicants' amendment of claims 1 (from which claim 12 depends) and 4 render the Examiner's objection moot. Amended claim 1 no longer recites "wild-type" because, as discussed above, the claims directed to Applicants' invention do not require this word. Applicants' request reconsideration and withdrawal of this objection.

Claim Rejections -- 35 U.S.C. § 112, second paragraph

Claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. The Examiner contends reference to "wild-type ATF2" is indefinite because it is the sole means of identifying the ATF2 polypeptide that is referred to by the claims. The Examiner acknowledges Applicants' reference to the December 1, 2005 telephonic interview, in which Applicants had referred to the sequence set forth in GenBank accession number NP_001871[1] as evidence that the sequence of normal human ATF2 was well known in the art since 1989. However, the Examiner states that in the specification there is no reference to a particular sequence. The Examiner also states that it is not clear to which particular polypeptide Applicants refer due to naturally-occurring polymorphism and alternative splicing of the gene encoding for ATF2. The Examiner contends that GenBank Accession No. AAH26175 has a different amino acid sequence than that of GenBank accession number NP_001871. The Examiner is of the opinion that this discrepancy could be resolved by reference to a specific amino acid sequence of ATF2, as referred to by the claims. These grounds for rejection are not well taken.

[1] In their December 9, 2005 Amendment, Applicants inadvertently referred to GenBank accession number NP_008171. The correct GenBank accession number is NP_001871, and will be referred to as this hereafter.

Applicants' amendment of claim 1 to cancel the word "wild-type" renders this part of the Examiner's rejection moot. As stated on page 20 of Applicants' December 9, 2005 Amendment, amended claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 refer to "wild-type ATF2" to clarify that this fragment is not mutated at residues 69 and 71. As stated above, it is clear in the specification as well as the claims that Applicants refer to N-terminal fragments of ATF2 having a normal or endogenous amino acid sequence.

The Examiner points to Crawford et al. (Annu. Rev. Genomics Hum. Genet. 2005; 6: 287-312) regarding polymorphisms of the ATF2 gene and Bailey et al.(J. Mol. Endocrinol. 2005 Feb; 34(1): 19-35) regarding alternative splicing of the ATF2 gene. Based upon these documents, the Examiner concludes that reference by Applicants to "wild-type ATF2" is not clear. Amended claim 1 no longer recites "wild-type." Applicants' reference to AFT2 in the instant application is clear.

Reference to AFT2, as used in the application, does not refer to variant or mutant sequences of the protein. It refers to the amino acid sequence of normal or endogenous ATF2. For example, on page 37, line 27 to page 38, line 1 of the instant application, on page 36, lines 8-9 of U.S. Provisional Application No. 60/269,118 and on page 36, lines 19-20 of U.S. Provisional Application No. 60/269,257, it states "[i]n still another embodiment, cells (such as human tumor cells) that express ATF2 endogenously can be used[2]." Based upon statements like this and reference throughout the specification to ATF2 absent any mention of mutations, a skilled worker would understand that the N-terminal fragments of ATF2 of the invention are derived from a normal, non-mutated ATF2 amino acid sequence. The specification clearly refers to N-terminal fragments derived from a non-mutated or non-variant ATF2 amino acid sequence. For these reasons, Applicants believe that the application as filed, as well as provisional applications 60/269,257 and 60/269,118 from which the current application claims benefit, are clear with respect to reference to ATF2.

[2] The application as filed inadvertently recites "sued" rather than "used". Applicants had intended recitation of "used".

The Examiner's contention that GenBank™ Accession No. AAH26175 has a different amino acid sequence than that of GenBank™ accession number NP_001871 is not true. The NP_001871 sequence comprises the AAH26175 sequence. In fact, NP_001871 comprises amino acid residues 1-505, while AAH26175 comprises amino acid residues 1-209 of the NP_001871 sequence. Accompanying this Amendment, Applicants direct the Examiner's attention to Exhibit 1, which is an alignment of both sequences. It is evident from this alignment that the two sequences are not different; in fact, amino acid residues 1-209 are identical in both sequences. A skilled worker would recognize that Applicants' teachings in the specification use a normal, non-mutated ATF2 amino acid sequence. A skilled worker would know that he or she could use a database like GenBank™ to locate an ATF2 amino acid sequence that is normal or non-mutated. In fact, the skilled worker would understand that any normal, non-mutated ATF2 amino acid sequence, such as the GenBank™ AAH26175 sequence or the GenBank™ NP_001871 sequence, may be used to practice Applicants' invention.

To the extent that the rejection is based upon the Examiner's concern that the application does not provide a sequence for the polypeptide referred to as "ATF2" that is more a written description concern than an indefiniteness one. Indeed, the Examiner's formulation of his rejection as "the specification does not appear to describe the amino acid sequences of the polypeptide designated 'ATF2'" (page 8, Office Action) seems directed to written description. Nonetheless, Applicants respectfully remind the Examiner that the Manual of Patent Examining Procedure (hereafter "MPEP") Section 2163.02 states: "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement." However the rejection is phrased, as explained above, the specification as it describes ATF2 would be understood by a skilled worker. It is clear that applicants' invention comprises a fragment of the full-length amino acid sequence of ATF2 that is normal or non-mutated.

The above remarks substantiate Applicants' position that to a skilled worker reference to ATF2, without reference to a particular sequence, is definite. For the above reasons, Applicants

request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 112, second paragraph, and allow amended claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43.

Claims 1, 4, 8-12 and 35-43 also have been rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. The Examiner contends that the term "Peptide II" is not clear. Applicants traverse.

Applicants believe it is clear from a reading of amended claim 1 that the inhibitory N-terminal fragment of wild-type ATF2 comprising amino acid residues 50-100 is also referred to in the application as Peptide II. Support for this reference may be found, for example, on page 39, line 17-19 and page 4, line 16-17 of the instant specification. Applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 112, second paragraph, and allow amended claims 1, 4, 8-12 and 35-43.

Claim 4 also has been rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. The Examiner contends that claim 4 incorrectly depends from claim 1 because an amino-terminal fragment of ATF2 cannot consist of both the ATF2 region spanning from about amino acid residue 50 to about amino acid residue 75, and also compromise an additional ATF2 region from about residue 76 to about amino acid residue 100.

To expedite prosecution, Applicants have amended claim 4 to recite as an independent claim, no longer depending from amended claim 1. Applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 112, second paragraph, and allow amended claim 4.

Claim Rejection -- 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1, 8-13, 15, 20, 21, 23-29, and 35-43 under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement. Specifically, the Examiner contends that the claims contain new matter because Applicants, in their December 9, 2005 Amendment, do not provide sufficient written support for the recitation of the term "wild-type

ATF2". The Examiner was not convinced by the support for this term provided in Applicants' December 9, 2005 Amendment. The Examiner also contends that the specification does not provide a nexus between "wild-type ATF2" and the sequence set forth in GenBank™ accession number NP_001871 that was referred to during Applicants' December 1, 2005 telephonic interview with the Examiner. The Examiner has advised Applicants that this rejection may be overcome upon a showing of necessary written support for "wild-type ATF2". Applicants traverse.

Applicants teach N-terminal fragments of an ATF2 amino acid sequence that are normal or non-mutated. Applicants' amendment of claim 1 to cancel the word "wild-type" obviates the Examiner's rejection. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 U.S.C §102

Claims 13 and 20 stand rejected under 35 U.S.C. § 102 (b) as "anticipated" by Livingstone et al. (EMBO J. 1995; 14(8): 1785-1797)(hereafter "Livingstone"). The Examiner alleges that Livingstone "teaches" a composition comprising an amino-terminal fragment of ATF2, which consists essentially of (i.e. comprises) amino acid residues from about residue 50 to about residue 100, and a pharmaceutically acceptable carrier or excipient. This ground for rejection is not well taken.

Applicants would like to point out that the terms "comprising" and "consisting essentially of" do not have the same legal meaning. The MPEP Section 2111.03 states that the transitional term "comprising" is: "inclusive or open-ended and does not exclude additional, unrecited elements or method steps." Whereas, according to the MPEP Section 2111.03: "[t]he transitional term 'consisting essentially of', limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention." Applicants respectfully point out that while the fragment taught by Livingstone comprises amino acid resides 1-112, it does not teach Applicants' invention. Livingstone is distinguishable from one aspect of Applicants' invention, which is a fragment that consists essentially of about amino acid residue 50 to about amino acid residue 100 of ATF2.

Furthermore, Livingstone teaches ATF2 sequences that are fused to Gal4 DNA binding domains. Such fused sequences are not suitable for administration to a subject in need thereof. Additionally, Livingstone does not teach fragments in a pharmaceutically acceptable carrier. On the other hand, Applicants teach N-terminal fragments of ATF2; not fragments that are fused to Gal4 DNA binding domains. The N-terminal fragments of ATF2 taught by Applicants are suitable for administration to a subject in need thereof. For anticipation, a document must disclose "each and every element of the claim". As Applicants explain above, Livingstone does not disclose the claimed N-terminal fragment(s) of ATF2. Furthermore, Livingstone does not teach or suggest ATF2 N-terminal fragments of claim 1 or 4. Thus, Livingstone does not and cannot anticipate claims 13 and 20. Accordingly, Applicants request that the Examiner reconsider and withdraw this rejection and allow claims 13 and 20.

Claims 1, 8-13, 20, and 35-43 stand rejected under 35 U.S.C. § 102 (a) as "anticipated" by Bhoumik *et al.* (Clin. Cancer Res. 2001 Feb; 7(2): 331-342)(hereafter "Bhoumik (2001)")and as evidenced by Bhoumik *et al.* (Proc. Natl. Acad. Sci. USA. 2004;101;4222-4227)(hereafter "Bhoumik (2004)"). The Examiner on page 6 of the Office Action asserts that claims 1, 4, 8-13, 15, 20. 21, 23-29 and 35-43 are not entitled to priority under 35 U.S.C. § 120 to the earlier filing dates of the priority documents. Applicants traverse.

As pointed out above, Applicants' amendment of claim 1 to cancel the word "wild-type" removes the Examiner's 35 U.S.C. § 112, first paragraph, rejection. Accordingly, Applicants' ability to rely upon the earlier filing dates removes the Examiner's anticipation rejection based upon Bhoumik (2001) as evidenced by Bhoumik (2004). Applicants respectfully request withdrawal of this rejection.

Claim Rejections - 35 U.S.C. §103

Claims 15 and 21 stand rejected under 35 U.S.C. § 103(a) as obvious over Livingstone in view of Nilsson et al. (Nucleic Acid Res. 1985; 13 (4): 1151-1162)(hereafter "Nilsson"). The Examiner contends that Livingstone teaches that which is set forth in the above rejection of claims

13 and 20 under 35 U.S.C. § 120(b). The Examiner further contends that Nilsson teaches fusion polypeptides comprising a foreign gene product and staphylcoccal protein A that are translocated through the cytoplasmic membrane with the aid of a signal sequence. Applicants traverse.

A finding of *prima facie* obviousness requires that the combined references teach or suggest all of the claim limitations. As discussed for the anticipation rejection *supra*, Livingstone does not teach the inhibitory N-terminal fragments of ATF2 of the present claims, and only teaches ATF2 sequences that are fused to Gal4 DNA binding domains.

Nilsson does not remedy the deficient teachings in the Livingstone and does not disclose or suggest the inhibitory N-terminal ATF2 fragments presently claimed. Therefore, Nilsson cannot be combined with Livingstone to arrive at the presently claimed invention.

Thus, Applicants traverse this rejection because neither Livingstone nor Nilsson teaches or suggests the inhibitory N-terminal fragment as recited in the amended claims, as such, combination of these references also cannot disclose the claimed fragments. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 23-29 stand rejected under 35 U.S.C. § 103(a) as obvious over Bhoumik (2001), as evidenced by Bhoumik (2004). The Examiner contends that Bhoumik (2001) teaches that which is set forth in the above rejection of claims 1, 8-13, 20, and 35-43 under 35 U.S.C. § 102(a). Applicants traverse.

The grounds for this obviousness rejection are based upon the same references addressed above in the context of the Examiner's rejection of claims 1, 8-13, 20, and 35-43 under 35 U.S.C. § 102 (a). Based upon Applicants' explanation above for removal of Bhoumik (2001) as a prior art reference, Applicants respectfully request withdrawal of this rejection.

Claims 15, 21, and 23-29 stand rejected under 35 U.S.C. § 103 (a) as obvious over Bhoumik (2001) in view of Mi et al. (Mol. Ther. 2000 Oct; 2 (4): 339-347)(hereafter "Mi"). The Examiner contends that Bhoumik (2001) teaches that which is set forth in the above rejection of

claims 1, 8-13, 20 and 35-43 under 35 U.S.C. § 102(a). The Examiner further contends that Mi teaches cationic peptides that facilitate efficient transduction of proteins *in vivo*, and that these peptides therapeutically facilitate rapid and efficient delivery of proteins into solid tumors. Applicants traverse.

Based upon Applicants' explanation above for removal of Bhoumik (2001) as a prior art reference, Mi is not available on its own to reject claims 15, 21 and 23-29. Mi does not teach any N-terminal fragments of ATF2, which consist of amino acid residues 50-100 of the full-length protein. Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: August 3, 2006

Respectfully submitted,

By _____

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